I concur with this review memo. I Wu 2/10/23

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch

BLA NUMBER:	STN #125771.000
DATE RECEIVED BY CBER:	06/30/2022
DATE REVIEW COMPLETED:	01/30/2023
PRODUCT:	ALTUVIIIO™ (efanesoctocog alfa or BIVV001)
APPLICANT:	Bioverativ Therapeutics Inc.
PROPOSED INDICATION:	Treatment of adults and children with Hemophilia A (congenital Factor VIII deficiency) for: (1) Routine prophylaxis to reduce the frequency of bleeding episodes; (2) On-demand treatment and control of bleeding episodes; (3) Perioperative management of bleeding.
PHARM/TOX REVIEWER:	Melek Sunay
PHARM/TOX BRANCH CHIEF:	Iwen Wu (Acting)
PRODUCT (CMC) REVIEWERS:	Zuben Sauna (Chair); Daniel Lagasse
CLINICAL REVIEWERS:	Megha Kaushal
PROJECT MANAGER:	Niloofar Kennedy
DIVISION DIRECTOR:	Tejashri Purohit-Sheth
OFFICE DIRECTOR:	Wilson Bryan

EXECUTIVE SUMMARY:

ALTUVIIIO™ (efanesoctocog alfa or BIVV001) is a recombinant fusion protein consisting of a single chain of B domain deleted (BDD) human coagulation Factor VIII (FVIII) covalently linked to the D'D3 domain of von Willebrand factor (VWF) via the Fc domain of human immunoglobulin G1 (IgG1) and 2 XTEN® polypeptides. Activated ALTUVIIIO™, which replaces missing or deficient endogenous FVIII, serves as a cofactor for activated factor IX in the intrinsic coagulation pathway. The covalently linked D'D3 domain of VWF prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII half-life imposed by VWF clearance. The inclusion of XTEN polypeptides alters the hydrodynamic radius of the

molecule, reducing its clearance and requiring less frequent administration compared to existing marketed products. The proposed label specifies that for routine prophylaxis, the recommended maximum clinical dose level/dosing regimen for ALTUVIIIO™ is 50 (International Units) IU/kg weekly. For on-demand treatment and control of bleeding episodes and perioperative management, the recommended dose level is 50 IU/kg/administration, every (b) (4) days.

The *in vitro* clotting activity of ALTUVIIIO™ in human plasma samples obtained from FVIII-depleted plasma or HemA patients was determined by measurement of activated partial thromboplastin time (aPTT) levels. *In vivo* pharmacodynamics (PD) were evaluated by single intravenous (IV) administration of ALTUVIIIO™ (37.5 to 150 IU/kg) in hemophilia A (HemA) mice following tail clip injury. Results demonstrated a dose-dependent reduction in bleeding times and blood loss similar to those seen in mice injected with Advate®, a full-length recombinant FVIII, that was used as a comparator.

Prophylactic activity was assessed in HemA mice administered a single IV administration of ALTUVIIIO™ (1.5-100 IU/kg) 72 hours prior to tail vein transection (TVT) compared to IV administered Advate® 24 hours prior to TVT. Based on the occurrence of spontaneous re-bleeding during the 24 hours post-TVT, ALTUVIIIO™ displayed a 3-fold prolongation of prophylactic activity relative to Advate® at all dose levels evaluated. This correlated with a 3-fold longer half-life ($T_{1/2}$) of ALTUVIIIO™ compared to Advate®. Comparable survival protection, measured as effective dose 50 (ED50; dose level that corresponded to 50% survival in animals 24 hours following TVT), was observed for ALTUVIIIO™ (7 IU/kg) and Advate® (9 IU/kg).

Pharmacokinetic (PK) and toxicokinetic (TK) assessments were performed following single and repeat IV administration of ALTUVIIIO™ in HemA mice, (b) (4) rats, and (b) (4) monkeys. Systemic exposure levels after a single administration of ALTUVIIIO™ in mice, rats and monkeys showed a dose-dependent proportional increases in maximum concentration (C_{max}) and area under the concentration-time curve (AUC). The terminal plasma half-life ($T_{1/2}$) of ALTUVIIIO™, which reflects the exposure and clearance of the fusion protein in plasma, was approximately 30 hours in mice and monkeys, and approximately 20 hours in rats. Overall, the $T_{1/2}$ of ALTUVIIIO™ was approximately 3-fold longer than Advate®.

A repeat-dose IV toxicity study in healthy adult (b) (4) rats administered 5, 250, and 750 IU/kg ALTUVIIIO™ every 3 days for 4 weeks did not result in any adverse findings and no evidence of thrombus formation was observed. The no observed adverse effect level (NOAEL) was the maximum dose level administered, 750 IU/kg/dose (15-fold higher than the maximum recommended prophylactic clinical dose level of ALTUVIIIO ™ [50 IU/kg once weekly]).

A repeat-dose IV toxicity study in healthy (b) (4) monkeys administered 25, 75, 250, 750 IU/kg ALTUVIIIO™ every 4 days for 4 weeks showed increased activated partial thromboplastin time (aPTT) values likely due to acquired hemophilia resulting from the development of anti-drug antibodies (ADAs) to ALTUVIIIO™. ADA-induced acquired hemophilia resulted in the death of one monkey on Day 30 due to excess bleeding following blood sample collection. There were no other adverse findings directly attributed to the pharmacologic activity/intended mechanism of ALTUVIIIO™.

A hemocompatibility study was conducted to evaluate the effect of ALTUVIIIO™ on hemolysis and plasma flocculation (turbidity) of human blood. Whole blood samples were collected from 3 healthy male and 3 healthy female human subjects. No hemolytic effect or flocculation was observed following *in vitro* treatment of human whole blood with ALTUVIIIO™ at 0.41, 1.2 and 4.1 μg/mL.

Genotoxicity, carcinogenicity, and developmental and reproductive (DART) toxicity studies were not conducted with ALTUVIIIO™. This is acceptable based on the product and its nonclinical safety profile.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There are no nonclinical deficiencies identified in this submission. There are no outstanding requests for additional nonclinical data for evaluation of ALTUVIIIO™. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry:

ALTUVIIIO™ is a lyophilized powder for reconstitution supplied in single-use glass vials containing 250, 500, 750, 1000, 2000, 3000, or 4000 International Units (IU), lyophilized powder in single-dose vials for reconstitution. The composition of the formulation excipients (10 mM histidine buffer, 250 mM arginine hydrochloride, 5% (w/v) sucrose, 5 mM calcium chloride dihydrate, 0.05% (w/v) polysorbate 80 prior to lyophilization is the same for all dosage strengths; only the quantity of ALTUVIIIO ™ varies. The powder for injection is reconstituted with sterile water for injection (sWFI) supplied in a prefilled syringe at a nominal volume of 3 mL. A vial adapter is also provided with the drug product vial and the sWFI prefilled syringe to aid in administration. The ALTUVIIIO™ drug product (DP) has a shelf life of 36 months from the date of manufacture when stored at room temperature (30°C) for up to 6 months in the primary container closure system. ALTUVIIIO™ is administered by IV injection after reconstitution.

Abbreviations

ADA	Anti-drug antibodies
aPTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration curve
CL	Clearance
Cmax	Maximum plasma concentration or activity
Cmax/Dose	Dose normalized maximum concentration or activity in plasma
DKO	Double knock-out
DP	Drug Product
ED50	Effective dose levels in 50% of animals
Fc	Fragment crystallizable region of IgG1

FcRn	Neonatal Fc receptor
FIX	Factor IX
FVIII	Factor VIII
GLP	Good laboratory practice
GMP	Good manufacturing practice
HemA	Hemophilia A
(b) (4)	(b) (4)
Hrs	Hours
IgG	Immunoglobulin G1
IHC	Immunohistochemistry
IV	Intravenous
IU	International units
(b) (4)	(b) (4)
LLOQ	lower limit of quantitation
M	Molar
Mins	Minutes
mL	Milliliter
MOA	Mechanism of action
MRT	Mean residence time
nM	nanomolar
NOAEL	No observed adverse effect level
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Prothrombin time
rFVIII	Recombinant Factor VIII
rFVIIIFc	Recombinant fusion protein comprising a BDD factor VIII and an Fc
(b) (4)	(b) (4)
Sec	Seconds
SD	Standard deviation
sWFI	Sterile water for injection
$T_{1/2}$	Terminal plasma half-life
TEAEs	Treatment-emergent adverse events
TK	Toxicokinetic(s)
TVT	Tail vein transection
µM	Micromolar
VWF	Von Willebrand Factor
XTEN polypeptides	Unstructured hydrophilic polypeptide, composed of repeating motifs of 6 natural amino acids (Gly, Ala, Pro, Glu, Ser, Thr or G,A,P,E,S,T). XTEN is registered trademark of Amunix Pharmaceuticals Inc.

Related File(s)

IND# 17464: Antihemophilic Factor (Recombinant), Fc-VWF-XTEN Fusion Protein, [BIVV001]; Treatment of adults and children 12 years of age and older with hemophilia A; Bioverativ Therapeutics Inc; ACTIVE

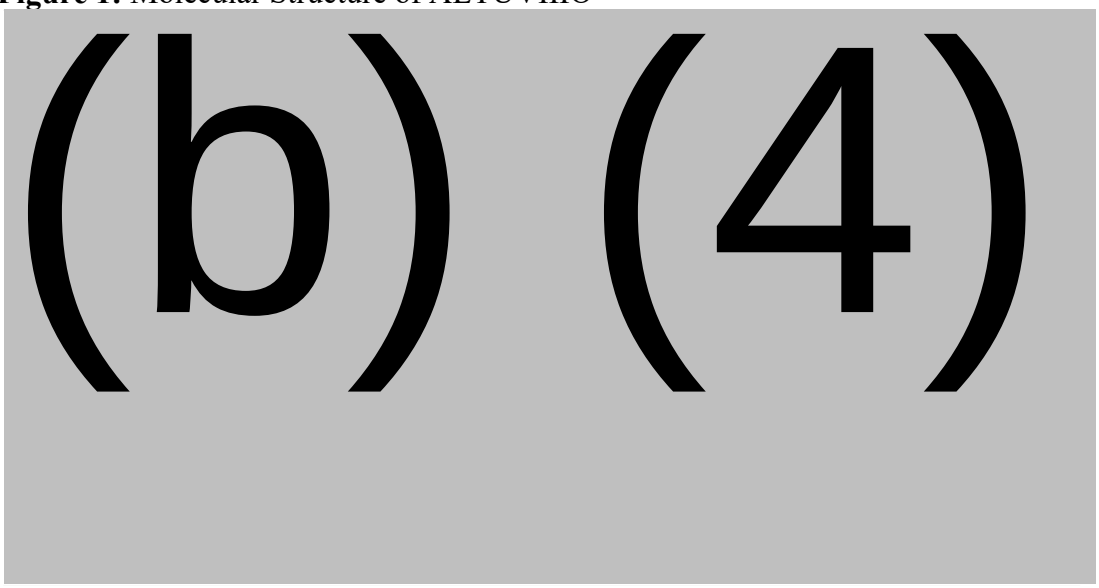
Table of Contents

INTRODUCTION

Target Disease: Hemophilia A is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 males. Mutations in the FVIII gene, which encodes a non-enzymatic cofactor for activated factor IX that is critical for fibrin clot formation, lead to deficiencies in coagulation. Depending on the residual activity of FVIII, disease severity is classified as mild (>5% to <40% of normal), moderate (1% to 5% of normal), or severe (<1% of normal). The disease is characterized by frequent, spontaneous internal bleeding, which can lead to chronic arthropathy (joint damage), intracranial hemorrhage, and/or death. There is no available cure for hemophilia A; treatment focuses on the replacement of FVIII with FVIII containing coagulation products to restore hemostasis. IV injection of plasma-derived or recombinant FVIII at the time of a bleed (i.e., on-demand therapy) or via a prophylactic regimen to prevent bleeding, are effective means to prevent and arrest abnormal bleeding; however, per the applicant, these regimens require frequent administrations to maintain high sustained FVIII activity levels throughout the dosing interval to improve bleed prevention and provide greater protection against joint damage resulting in a high burden on patients to comply with routine administrations.

Product/Chemical Structure (description obtained from Module 2.4.): ALTUVIIIO™ is a recombinant fusion protein consisting of a single chain B domain deleted human FVIII covalently linked to the D'D3 domain of VWF via the Fc domain of IgG1 and 2 XTEN polypeptides. XTEN® polypeptides are unstructured hydrophilic polypeptides, composed of repeating motifs of 6 natural amino acids [Glycine, Alanine, Proline, Glutamic acid, Serine and Threonine]. The D'D3 domain of VWF is the region that interacts with FVIII. The D'D3 domain of VWF was appended to the rFVIII-Fc fusion protein to prevent rFVIII interaction with endogenous VWF, thus, overcoming the limitation on FVIII. The first XTEN polypeptide is inserted in between FVIII N745 and E1649 amino acid residues, replacing the natural FVIII B domain. It is flanked by natural FVIII thrombin cleavage sites (i.e., a2 on the N terminus and a3 on the C terminus), resulting in its release upon ALTUVIIIO™thrombin activation. The second XTEN polypeptide is inserted in between the D'D3 and Fc (fragment crystallizable region of IgG1). (b) (4) Additionally , the inclusion of XTEN polypeptides is expected to alter the hydrodynamic radius of the molecule, reducing its clearance, thus requiring less frequent administration compared to existing marketed products.

Figure 1: Molecular Structure of ALTUVIIIO™



Fc: fragment crystallizable region of IgG1; FcRn: neonatal Fc receptor; FVIII: factor VIII; VWF: von Willebrand factor; a1, a2 and a3: FVIII acidic region1, 2 and 3; XTEN polypeptide: unstructured polypeptides, composed of repeating motifs of 6 natural amino acids (G, A, P, E, S, T). Solid lines indicate XTEN polypeptides.
Source: Nonclinical Overview; Module 2.4 in the BLA.

Upon thrombin activation, the interaction between FVIII and the D'D3 domain of VWF is disrupted, releasing D'D3-XTEN (similar to the release of endogenous full length VWF from FVIII) and yields activated rFVIII and Fc fusion protein. The activated rFVIII replaces missing or deficient endogenous FVIII and serves as a cofactor for activated factor IX in the intrinsic coagulation pathway. Per the applicant, ALTUVIIIO™ activity is independent of endogenous VWF which extends the half-life by decoupling FVIII from VWF-mediated clearance.

NONCLINICAL STUDIES

***Reviewer's Notes*:**

- *The applicant has used the terms BIVV001, efanesoctocog alfa (INN), recombinant coagulation factor VIII Fc-von Willebrand factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN), or BIIB073 interchangeably, in the nonclinical study reports. This reviewer refers to ALTUVIIIO™ as BIVV001 throughout the 'Nonclinical Studies' section.*

- *The applicant utilized the murine FVIII knockout (KO) hemophilia A model (HemA mice) for in vivo pharmacology and PK studies. HemA mice have less than 1% of endogenous FVIII activity and exhibit prolonged clotting times, similar to severe hemophilia A patients and are the most commonly used and pharmacologically relevant model to assess hemostatic potential of hemophilia A therapeutics in nonclinical studies. Additionally, the murine FVIII protein is about 74% identical to the human FVIII (hFVIII), thus administration of hFVIII variants restores clotting in these mice.*

- *Advate® was used as the comparator FVIII molecule in many nonclinical pharmacology and PK studies. Per the applicant, Advate® was selected as a comparator protein because there is extensive PK data available with Advate® across the species evaluated.*

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology studies were conducted to support the rationale for the administration of BIVV001 in the proposed clinical indication.

In Vitro Studies

Study Number	Study Title / Publication Citation	Report Number
1	Evaluation of recombinant FVIIIFc-VWF-XTEN (BIVV001) activity in one-stage clotting and chromogenic assays	R-BV001-03
2	Thrombin generation, Whole blood clotting and fibrin generation profiles of recombinant FVIIIFc-VWF-XTEN (BIVV001)	R-BV001-04
3	Comparison of (b) (4) Kinetics of BIVV001 and BDD FVIII By (b) (4)	R-BV001-07
4	(b) (4) Analysis of (b) (4) Recombinant FVIIIFc-XTEN-VWF (BIVV001)	R-BV001-10

In Vivo Studies

Study Number	Study Title / Publication Citation	Report Number
5	Prophylactic efficacy of BIVV001 in the hemophilia A mouse tail vein transection model	R-BV001-05
6	Acute efficacy of BIIB073 in the tail clip bleeding model of hemophilia A mice	Rsch-2015-043

Overview of Pharmacology Studies

Overview of In Vitro Studies

Study #1
Evaluation of Recombinant FVIIIFc-VWF-XTEN (BIVV001) Activity in One-Stage Clotting and Chromogenic Assays (Non-GLP; Study Report # R-BV001-03; Bioverativ, MA, USA)

Objective:
This study evaluated the clotting activity of BIVV001 by aPTT assay and chromogenic assay.

Methods:

One-stage clotting (aPTT) assay:

(b) (4)

***Reviewer's Notes*:**

- *aPTT assay measures the time elapsed following the addition of calcium to the formation of a fibrin clot by* (b) (4)
- *The aPTT-based FVIII one-stage clotting assay quantifies the ability of FVIII products to restore clotting activity of FVIII-deficient plasma. Per the applicant, this assay is widely used to detect the amounts of FVIII activity in samples from patients treated with replacement FVIII products and it has been the preferred assay for PK assessments in the clinical setting.*

(b) (4) **(Chromogenic) assay**:

(b) (4)

***Reviewer's Note*:**

- *The FVIII Chromogenic assay* (b) (4) *measures FVIII activity by determination of the rate of activation of Factor X (activated Factor X (FXa)) in a sample via a chromogenic substrate.* (b) (4)

  This step is stimulated by FVIII, thus the rate of activation of Factor X is solely dependent on the amount of FVIII present. This assay, is specific for human clotting factor components, can be used in hemophilic animals because these animals lack endogenous FVIII.

Results:

- The molar specific activity of BIVV001 (b) (4) was lower than Advate® (b) (4) (b) (4) when evaluated in the one-stage clotting assay. Per the study report, the decreased activity of BIVV001 could be due to the two thrombin cleavage steps necessary to activate BIVV001, resulting in prolonged clotting times for BIVV001 in the aPTT assay.

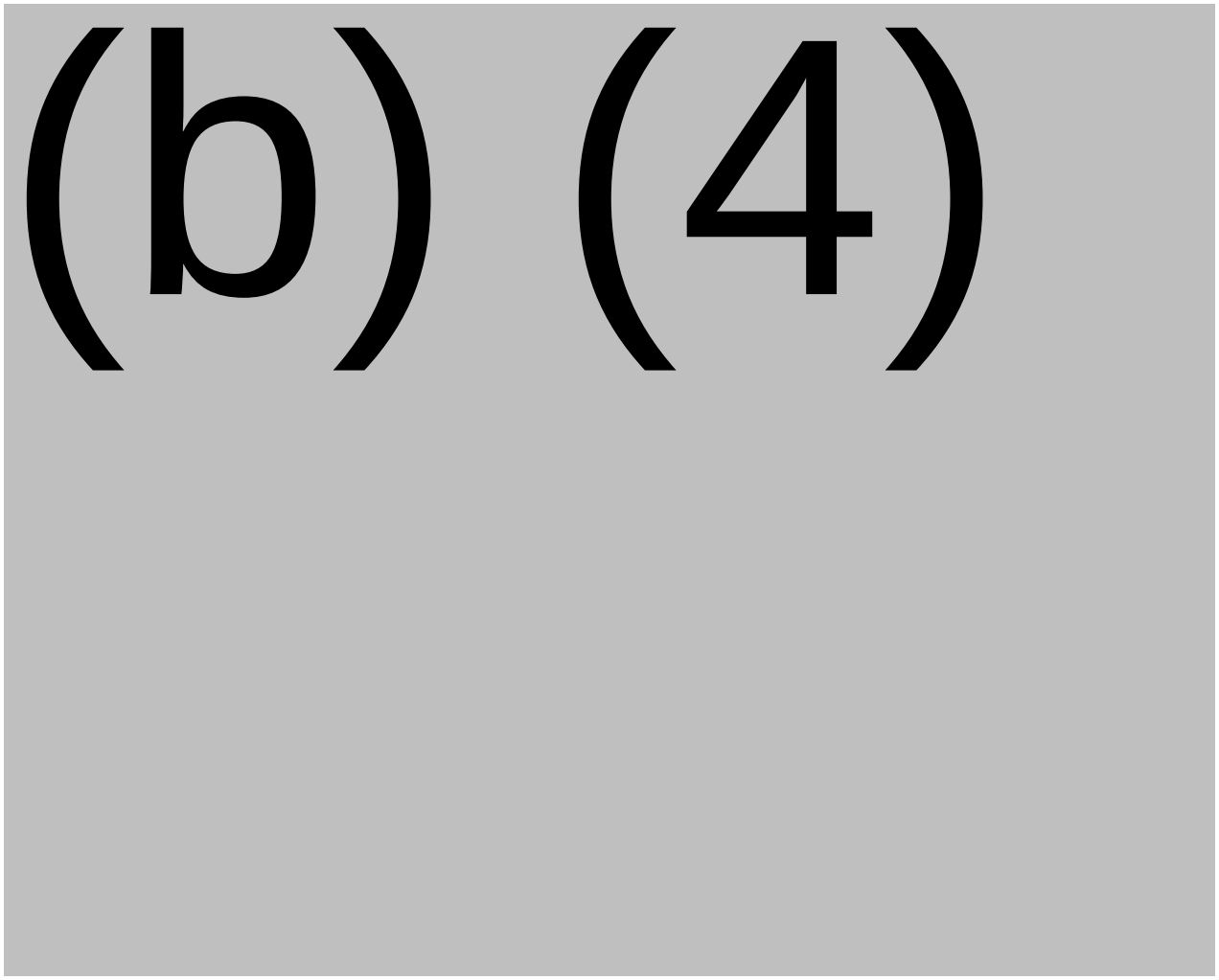
- The activity was similar between BIVV001 (b) (4) and Advate® (b) (4) (b) (4) when evaluated by (b) (4) chromogenic assay.

- Taken together, these results show that the activities of BIVV001 (b) (4) and Advate® (b) (4) were in the range previously reported for FVIII products (b) (4) (b) (4) for Advate®[1]; (b) (4) for Eloctate/Elocta[2] demonstrating that BIVV001 is fully functional once it is activated.

Study #2
Thrombin Generation, Whole Blood Clotting and Fibrin Generation Profiles of Recombinant FVIIIFc-VWF-XTEN (BIVV001) (Non-GLP; Study Report # R-BV001-04; (b) (4) USA)

Objective:
This study evaluated the hemostatic potential of BIVV001 by (b) (4) (b) (4) and (b) (4)

Methods:



[1] Advate Canadian Product Monograph. Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (rAHF-PFM) 250, 500, 1000, 1500, 2000 and 3000 International Units (IU) per vial. Baxter Corporation. 2013 December 19.
[2] Eloctate Canadian Product Monograph. Biogen Canada Inc. 2016 July.

***Reviewer's Note*:**

- *Human platelet-poor FVIII-deficient plasma used in this study was derived from congenital FVIII-deficient whole blood drawn from Hemophilia A donors who underwent a certain period of washout (*(b) (4) *depending on treatment regimen) to ensure* (b) (4) *FVIII activity (confirmed by FVIII chromogenic assay).*

Results:

- BIVV001 showed thrombin activation kinetics and whole blood clotting potential comparable to Advate® when analyzed at similar FVIII activity levels.

Study #3
Comparison of (b) (4) **Kinetics of BIVV001 and BDD FVIII by** (b) (4) **(**Non-GLP; Study Report # R-BV001-07; (b) (4) USA)

Objective:
This study evaluated 1) thrombin activation kinetics of BIVV001 compared with in-house generated B-domain deleted rFVIII (BDD FVIII), and 2) compared the kinetics of thrombin cleavage at the site introduced between D'D3-XTEN and Fc relative to cleavage of FVIII.

Methods:

(b) (4)

Study #4
(b) (4) **Analysis of** (b) (4) **Recombinant FVIIIFC-XTEN-VWF (BIVV001)** (Non-GLP; Study Report # R-BV001-10; (b) (4) USA)

Objective:
This study analyzed thrombin digestion of BIVV001 to evaluate consistency between the GMP batch drug substance (DS) and the interim reference standard (IRS).

Methods:

(b) (4)

Overview of *In Vivo* Studies

Study #5

Report Number		R-BV001-05
Date Report Signed		03/31/2017
Title		Prophylactic Efficacy of BIVV001 in the Hemophilia A Mouse Tail Vein Transection Model
GLP Status		No
Testing Facility		Bioverativ; Waltham, MA
Objective(s)		To evaluate the prophylactic activity of BIVV001 in comparison to Advate® in the tail vein transection (TVT) bleeding model in FVIII-deficient (HemA) mice.
Study Animals	**Strain/Breed**	Factor VIII KO (HemA) mice
	Species	Mouse
	Age	8-10 weeks old
	Body Weight	20-29 grams (gm)
	# males/group	7/group/timepoint
	Total #	254
Test Article		BIVV001; Lot# (b) (4)

<table>
<tr><td>Control Articles</td><td>Advate®; Lot#(b) (4)
Vehicle; Lot# not provided</td></tr>
<tr><td>Route of Administration</td><td>IV</td></tr>
<tr><td>Description of the Disease Model</td><td>HemA mice – FVIII KO mice</td></tr>
<tr><td>Study Groups and Dose Levels</td><td>
<table>
<tr><th>Group</th><th>Test/Control Article</th><th>Dose Level (IU/kg)</th><th>IV injection Dates and # of animals/group/date</th><th>Time (hr) post-administration to TVT</th></tr>
<tr><td>1</td><td rowspan="5">BIVV001</td><td>100</td><td>2/13/2017 (n=20)</td><td rowspan="6">72</td></tr>
<tr><td>2</td><td>50</td><td>12/12/2016 (n=7)
12/19/2016 (n=7)
1/30/2017 (n=7)
2/13/2017 (n=10)</td></tr>
<tr><td>3</td><td>15</td><td rowspan="3">12/12/2016 (n=7)
12/19/2016 (n=7)
1/30/2017 (n=7)</td></tr>
<tr><td>4</td><td>5</td></tr>
<tr><td>5</td><td>1.5</td></tr>
<tr><td>6</td><td>Vehicle</td><td>0</td><td>12/12/2016 (n=7)
12/19/2016 (n=7)
1/30/2017 (n=7)
2/13/2017 (n=5)</td></tr>
<tr><td>7</td><td>Advate®</td><td>100</td><td>2/15/2017 (n=5)</td><td rowspan="5">24</td></tr>
<tr><td>8</td><td rowspan="4"></td><td>50</td><td>2/15/2017 (n=20)
12/14/2016 (n=7)
12/21/2016 (n=7)
02/01/2017 (n=7)</td></tr>
<tr><td>9</td><td>15</td><td rowspan="2">12/14/2016 (n=7)
12/21/2016 (n=7)
02/01/2017 (n=7)</td></tr>
<tr><td>10</td><td>5</td></tr>
<tr><td>11</td><td>1.5</td><td>12/14/2016 (n=7)
12/21/2016 (n=7)
02/01/2017 (n=7)</td></tr>
</table>
Reviewer's Notes:

Per the study report, due to the large number of animals used in the study, animals were divided into four identical cohorts (7 mice/group) and evaluated over 8 weeks of time at the dates indicated in the table above.
Per the applicant, the time between the administration of test or control articles and TVT was based on the reported 3-fold longer half-life ($T_{1/2}$) of BIVV001 compared to Advate® in HemA mice that was determined from Study #8 (Study Report # R-BV001-01).

</td></tr>
<tr><td>Dosing Regimen</td><td>Single</td></tr>
<tr><td>Randomization</td><td>Yes; based on body weight and age</td></tr>
<tr><td>Description of Masking</td><td>Not provided</td></tr>
<tr><td>Scheduled Sacrifice Time Points</td><td>9-12 hrs post-tail resection if excessive blood loss was noticed or at 24 hrs post-tail injury</td></tr>
</table>

***Key Evaluations and Assessments**:*

- The lateral tail vein was transected (where it was 2.7 mm thick) at 24 hrs (Advate®) or 72 hrs (BIVV001) post-dose, and the time to stop bleeding was recorded. The animal was then returned to a clean cage with white paper bedding. The time to spontaneous re-bleed and survival were monitored hourly for 9-12 hrs, followed by a final observation 24 hrs post-TVT.

***Key Results**:*

- Animals administered BIVV001 and Advate® resolved TVT-induced bleeding similarly (Table 1) when BIVV001 was administered 72 hours prior to TVT and Advate® was administered 24 hours prior to TVT. This demonstrates that the 3-fold increase in $T_{1/2}$ observed in Study #8 (Study Report #R-BV001-01) also corresponds to a 3-fold prolongation of prophylactic activity.

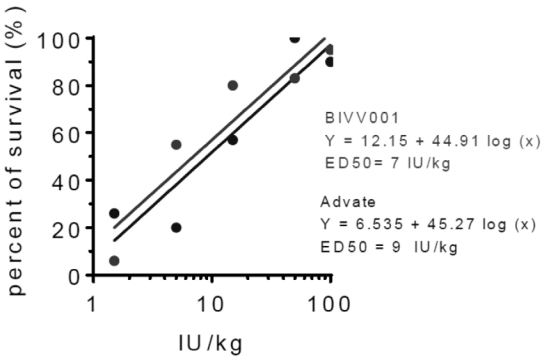
Table 1: Re-bleed within 24 hours (hrs) post TVT injury of BIVV001 (72 hrs pre-treatment) or Advate® (24 hrs pre-treatment) dosing groups compared to vehicle

	BIVV001 (72hr pre-treatment)					**Advate® (24hr pre-treatment)_**					**Vehicle**
Dose Level (IU/kg)	100	50	15	5	1.5	100	50	15	5	1.5	0
# Animal	20	30	20	20	18	20	28	21	20	19	25
# non re-bleed	15	13	5	3	3	14	10	2	1	4	1
% Non re-bleed animals	75	42	25	15	17	70	36	10	5	21	4

Source: Report No. R-BV001-05; Module 4.2.1.1 in the BLA

- Mean ED50 (extrapolated from dose-response for 24 hours post-TVT survival rate, Figure 2)
  - BIVV001: 7 IU/kg
  - Advate®: 9 IU/kg

Figure 2: Survival within 24 hrs post-TVT injury of BIVV001 or Advate® dosing groups compared to vehicle



The top line shows the percent survival vs. dose level for BIVV001. The bottom line shows the percent survival vs. dose level of Advate®.

Source: Report No. R-BV001-05; Module 4.2.1.1 in the BLA

Study #6

Report Number		Rsch-2015-043
Date Report Signed		01/31/2017
Title		Acute efficacy of BIIB073 in the tail clip bleeding model of hemophilia A mice
GLP Status		No
Testing Facility		Sanofi Research & Development (Former Bioverativ); Waltham, MA
Objective(s)		To evaluate the acute efficacy of BIVV001 in comparison to Advate® in the tail clip bleeding model of HemA mice
Study Animals	**Strain/Breed**	Factor VIII KO (HemA) mice or (b) (4)
	Species	Mouse
	Age	HemA mice: 9-14 weeks old (b) (4) mice: 7 weeks
	Body Weight	19-27 gm
	# males/group	14/group; 7/timepoint
	Total #	113 • 98 HemA mice • 15 (b) (4) mice
Test Article		BIVV001; Lot# (b) (4) ***Reviewer's Note*:** *Lot#* (b) (4) *is a research lot that has* (b) (4) *residues that were part of a restriction enzyme site in second XTEN that was inserted in between the D'D3 and Fc. Per the applicant, these residues did not impact the PD nor PK of the molecule and were removed from the clinical lot (Lot#* (b) (4) *) of BIVV001.*
Control Articles		Advate®; Lot# (b) (4) Vehicle; custom post-reconstitution diluent; Lot# not provided in the report
Route of Administration		IV injection; tail vein
Description of the Disease Model		HemA mice (b) (4) healthy mice were used as control

<table>
<tr><td>Study Groups and Dose Levels</td><td>
<table>
<tr><th>Dosing Date</th><th>Test/Control Article</th><th>Dose Level (IU/kg)</th></tr>
<tr><td rowspan="6">07/21/2015</td><td rowspan="3">BIVV001</td><td>150</td></tr>
<tr><td>75</td></tr>
<tr><td>37.5</td></tr>
<tr><td rowspan="3">Advate®</td><td>150</td></tr>
<tr><td>75</td></tr>
<tr><td>37.5</td></tr>
<tr><td rowspan="6">07/23/2015</td><td rowspan="3">BIVV001</td><td>150</td></tr>
<tr><td>75</td></tr>
<tr><td>37.5</td></tr>
<tr><td rowspan="3">Advate®</td><td>150</td></tr>
<tr><td>75</td></tr>
<tr><td>37.5</td></tr>
</table>
Reviewer's Notes:
➢ A group of HemA mice (n=14) were dosed with Vehicle and evaluated as negative controls and a group of (b) (4) mice (n=15) were evaluated to establish a protection baseline; it is not clear in the report which date the control animal data was collected.
➢ Per the study report, due to the large number of animals used on the study, the assessments were performed over two days. The dosing dates of each study group are listed in the above table.
</td></tr>
<tr><td>Dosing Regimen</td><td>Single</td></tr>
<tr><td>Randomization</td><td>Yes; based on body weight and age</td></tr>
<tr><td>Description of Masking</td><td>Not provided</td></tr>
<tr><td>Scheduled Sacrifice Time Points</td><td>Following the final blood collection</td></tr>
</table>

Key Evaluations and Assessments*:*

- Blood loss measurement: Tail clipping (5 mm from the tip) was performed at 5 minutes post-dose, immediately followed by blood collection for 30 minutes. Collection tubes were weighed before and after blood was collected.
- FVIII activity determined by aPTT assay

Key Results:

- Dose-dependent decrease in mean blood loss was observed and the decrease was comparable between BIVV001 and Advate® (Table 2).

Table 2: Mean blood loss volume (mL) per dosing group following tail clip injury

	BIVV001			**Advate®**			**Vehicle**	(b) (4)
Dose Level (IU/kg)	150	75	37.5	150	75	37.5	0	0
Mean Blood Loss Volume (mL) ± SD	0.207 ±0.19	0.299 ± 0.24	0.336 ± 0.25	0.231 ± 0.25	0.315 ± 0.22	0.422 ± 0.31	0.765 ± 0.23	0.069 ± 0.05

SD = Standard deviation
Source: Report No. Rsch-2015-043; Module 4.2.1.1 in the BLA

- Dose-dependent protection rate from bleeding; comparable between BIVV001 and Advate® (Table 3).

Table 3: Percent (%) of mice protected in each dosing group 30 minutes post-administration with BIVV001 or Advate®.

Dose Level (IU/kg)	BIVV001	Advate®
150	73	67
75	53	40
37.5	40	40

Source: Report No. Rsch-2015-043; Module 4.2.1.1 in the BLA

***Reviewer's Notes*:**

- *Per the study report, the "protection baseline" was determined by the mean volume of blood loss + 2 SD of healthy* (b) (4) *mice (n=15) that underwent the tail clipping procedure. Experimental mice with blood loss lower than this volume post-dosing were considered "protected."*
- *Vehicle-dosed animals were not protected and therefore not included in the table.*

PHARMACOKINETIC STUDIES

Summary List of PK Studies

In Vivo Studies

Study Number	Study Title / Publication Citation	Report Number
7	Pharmacokinetic evaluation of BIVV001 (b) (4) in HemA mice	R-BV001-02
8	Single dose pharmacokinetics studies of BIVV001 (Lot (b) (4)) in hemophilia A mice	R-BV001-01
9	Pharmacokinetics Studies of 8118073 in Hemophilia A Mice	Rsch-2015-044
10	The Pharmacokinetic Profile of Recombinant FVIIIFc-VWF-XTEN Is Independent from Endogenous VWF Levels in the Experimental Mouse Models	R-BV001-11
11	Comparability Pharmacokinetics Study of three batches of BIVV001 (rFVIIIFc-VWF-XTEN) in Hemophilia A Mice: (b) (4) (b) (4)	R-BV001-14
12	BIIB073: An Acute Intravenous Injection Pharmacokinetic Study in Male (b) (4) Rats	PD15-118
13	BIIB073: An In Vivo Assessment of Pharmacokinetics Following Intravenous Administration in Male (b) (4) Monkeys	P073-16-03

***Reviewer's Note*:**

- *Study No. 9 compared the PK profile following a single IV administration or subcutaneous administration of 25, 50, or 100 IU/kg of BIVV001 to IV administration of 25, 50, or 100 IU/kg Advate® in male HemA mice. The critical design elements of Study No. 9 are very similar to Study No. 8 with the exception of the additional subcutaneous route of*

administration (ROA), which does not reflect the clinical route of administration of ALTUVIIIO™. Therefore, no summary of Study No. 9 is provided in this review memo.

Overview of PK Studies

Study #7

Report Number		R-BV001-02
Date Report Signed		02/28/2017
Title		Pharmacokinetic evaluation of BIVV001 (b) (4) in HemA mice
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To confirm the half-life of BIVV001 and to determine the appropriate FVIII activity assay for PK analysis.
Study Animals	**Strain/Breed**	Factor VIII KO (HemA) mice
	Species	Mouse
	Age	14 weeks old
	Body Weight	23-27 gm
	# males/group	3/group
	Total #	6
Test Article		BIVV001; Lot #(b) (4) ***Reviewer's Note*:** ➢ *Lot#* (b) (4) *is research lot derived from the manufacturing cell line* (b) (4) *that was selected for development of the clinical lot.*
Route of Administration		IV injection; tail vein
Description of the Disease Model		HemA mice
Study Groups and Dose Levels		2 Groups; 200 IU/kg • Group 1: Plasma collection at 5 min, 48 hr, and 96 hr post-dose • Group 2: Plasma collection at 24, 72, and 120 hr post-dose
Dosing Regimen		Single
Randomization		Not provided
Description of Masking		Not provided
Scheduled Sacrifice Time Points		Not specified in the report.

Key Evaluations and Assessments:

- FVIII activity determined by aPTT and chromogenic assays
    - 100µl blood collected via retro orbital collection

Key Results:

- Half-life ($T_{1/2}$) of BIVV001 is comparable in both aPTT and chromogenic assays:
    - aPTT assay: 28.2 hours
    - Chromogenic assay: 28.6 hours

Overall conclusions from the study report:

The results of this study demonstrated the terminal half-life of BIVV001 to be approximately 28 hours which was comparable in both aPTT and chromogenic assays used to assess the FVIII activity. Therefore, a single FVIII activity assay for sample analysis would be sufficient to support PK analysis of BIVV001.

Study #8

Report Number		R-BV001-01
Date Report Signed		03/16/2017
Title		Single dose pharmacokinetics studies of BIVV001 (Lot (b) (4)) in hemophilia A mice
GLP Status		No
Testing Facility		Sanofi Research & Development (Former Bioverativ); Waltham, MA
Objective(s)		To compare the single dose PK profile of the clinical lot of BIVV001 (100, 50, or 25 IU/kg) to single dose PK profile of Advate® (100 IU/kg) in Hem A mice.
Study Animals	**Strain/Breed**	Factor VIII KO (HemA) mice
	Species	Mouse
	Age	HemA mice: 10-15 weeks old
	Body Weight	20-30 gm
	# males/group	3/group/timepoint
	Total #	84
Test Article		BIVV001; Lot# (b) (4)
Control Articles		Advate®; Lot# (b) (4)
Route of Administration		IV injection; tail vein
Description of the Disease Model		HemA mice

Study Groups and Dose Levels

Test/Control Article	Dose Level (IU/kg)	Plasma Collection Timepoints Post-Dose (hrs)
BIVV001	100	0.0833, 7, 24, 48, 72, 96, and 120
	50	
	25	
Advate®	100	0.0833, 4, 7, 16, 20, 24, and 32

Dosing Regimen	Single
Randomization	Yes; based on body weight and age
Description of Masking	Not provided
Scheduled Sacrifice Time Points	Following the final blood collection

Key Evaluations and Assessments*:*

- FVIII activity was determined by chromogenic assay
- PK profile
    - Blood samples were collected via descending vena cava collection (terminal procedure)

Key Results:

- FVIII plasma activity increased proportionally to BIVV001 dose level. Equivalent dose levels of BIVV001 and Advate® resulted in similar FVIII activity.
- PK analysis:

Table 4: PK parameters of IV dosed BIVV001 and Advate® in HemA mice

Test/Control Article	Target Dose Level (IU/kg)	Actual Dose Level* (IU/kg)	$T_{1/2}$ (hr)	C_{max} (IU/mL)	CL (mL/hr/kg)	MRT (hr)
BIVV001	25	59.45	31.24	1181.77	1.39	43.22
	50	109.05	30.20	2342.80	1.29	42.56
	100	222.35	25.01	50003.96	1.26	34.78
Mean ± SD			28.82 ±3.34	N/A	1.32±0.07	40.19 ± 4.96
Advate®	100	99.50	10.19	2652.43	4.47	11.65
Fold Increase in BIV001 compared to Advate®			2.8	Not provided	3.39	3.45

$T_{1/2}$: half-life; $C_{max:}$ maximum plasma activity occurring at T_{max}; CL: clearance; MRT: Mean residence time; * The actual dose level was determined in the dosing solution by chromogenic assay
Source: Report No. R-BV001-01; Module 4.2.2.7 in the BLA

Overall conclusions from the study report:
Single injection of BIVV001 in HemA mice resulted in 2.8-fold increase in $T_{1/2}$ and equivalent clotting activity compared to Advate®.

Study #10

Report Number		R-BV001-11
Date Report Signed		03/28/2017
Title		The Pharmacokinetic Profile of Recombinant FVIIIFc-VWF-XTEN is Independent from Endogenous VWF Levels in the Experimental Mouse Models
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To assess the relationship between the half-life of BIVV001 and endogenous VWF levels by: 1) evaluating the BIVV001 PK profiles in three different mouse models with varying levels of endogenous VWF, and 2) comparing the PK profiles of BIVV001 to two other rFVIII molecules (standard half-life rFVIII and an extended half-life rFVIIIFc).
Study Animals	**Strain/Breed**	• HemA mice • VWF heterozygous mice • FVIII/VWF double knock out (DKO) mice
	Species	Mouse
	Age	8-14 weeks
	Body Weight	23-27 gm
	# mice/group	• 3-4/group; sex not specified in the report • For VWF (b) (4) only: 5M/5F/group
	Total #	Not specified in the report

<table>
<tr><td>Test Articles</td><td>

rFVIII: Study# 897 and Study#1438: Xyntha, Lot# (b) (4); Study 1022: no lot number provided in the report.
rFVIIIFc: Study# 1084: Lot# (b) (4); Study# 1103: Lot# (b) (4) (RVS2 2000); Study# 1438; Lot# (b) (4)
BIVV001 (construct (b) (4)); All studies: Lot# (b) (4)

Reviewer's Note:

BIVV001 construct (b) (4) is the precursor of BIVV001 and differs by (b) (4) amino acids from the final BIVV001 that is used in the clinical product. Per the applicant, removal of these amino acids do not impact the PK or PD of the protein.

</td></tr>
<tr><td>Route of Administration</td><td>IV</td></tr>
<tr><td>Description of the Disease Model</td><td>

HemA mice (FVIII$^{-/-}$/VWF$^{+/+}$): 100% of circulating endogenous VWF
VWF deficient mice (FVIII$^{-/-}$/VWF$^{-/+}$): 37% of circulating endogenous VWF
DKO mice (FVIII$^{-/-}$/VWF$^{-/-}$): no circulating VWF

</td></tr>
<tr><td>Study Groups and Dose Levels</td><td>
<table>
<tr><td></td><td>Mouse Strain</td><td>HemA mice</td><td>VWF Het</td><td>DKO Mice</td></tr>
<tr><td rowspan="2">rFVIII</td><td>Study # (Date)</td><td>Study 897
(2/8-2/11/10)</td><td>Study 1414
(3/3-3/5/15)</td><td>Study 1022
(7/26-8/09/11)</td></tr>
<tr><td>Dose Level
(# animals / group)</td><td>125 IU/kg
4</td><td>218 IU/kg
3</td><td>144 IU/kg
4</td></tr>
<tr><td rowspan="2">rFVIIIFc</td><td>Study # (Date)</td><td>Study 1084
(12/13-12/18/10)</td><td>Study 1438
(4/27-5/3/2015)</td><td>Study 1104
(1/30-2/3/2012)</td></tr>
<tr><td>Dose Level
(# animals / group)</td><td>185 IU/kg
4</td><td>258 IU/kg
3</td><td>200 IU/kg
3</td></tr>
<tr><td rowspan="2">BIVV001</td><td>Study # (Date)</td><td>Study 1411
(2/23-2/28/2015)</td><td>Study 1438
(4/27-5/3/2015)</td><td>Study 1439
(4/27-5/3/2015)</td></tr>
<tr><td>Dose Level
(# animals / group)</td><td>197 IU/kg
3</td><td>200 IU/kg
3</td><td>201 IU/kg
3</td></tr>
</table>
Reviewer's Notes:

This report contains data from several sub-studies; the study groups, test articles, dose levels, and study dates are listed in the table above.
The test articles were administered to separate groups of mice on separate dates and analyzed at different timepoints for each rFVIII protein administered. The rationale for this study design was not provided in the report.
Plasma VWF was evaluated from 10 non-dosed mice (5M/5F) from each genetic background. It is not clear from the report if the same 10 animals were then dosed with the rFVIII proteins or if a separate group of animals was used.

</td></tr>
<tr><td>Dosing Regimen</td><td>Single</td></tr>
<tr><td>Randomization</td><td>Yes; based on body weight and age</td></tr>
<tr><td>Description of Masking</td><td>Not provided</td></tr>
<tr><td>Scheduled Sacrifice Time Points</td><td>At the time of blood collection</td></tr>
</table>

Key Evaluations and Assessments*:*

- VWF level in the plasma was determined by VWF (b) (4)

- FVIII activity was determined by chromogenic assay
- PK profile was determined by noncompartmental analysis [NCA]
    - Blood samples were collected via inferior vena cava collection (terminal procedure)

Key Results:

- Circulating plasma VWF levels reflected the genetic background (VWF status) of the animal models in non-dosed mice (Table 5).

Table 5: Plasma VWF levels (ug/mL) in non-dosed HemA, VWF Het, and DKO mice

Animal ID		1	2	3	4	5	6	7	8	9	10
Gender		M	M	M	M	M	F	F	F	F	F
Plasma VWF Level (µg/mL)	**HemA**	82	79	85	81	75	83	89	78	71	76
	VWF heterozygous	31	30	28	29	32	32	28	27	30	33
	DKO	BELOW DETECTION LIMIT									

Source: Report No. R-BV001-11; Module 4.2.2.7 in the BLA

- The FVIII activity recovery rate (% of initial dose of BIVV001) was increased compared to rFVIIIFc or rFVIII across models.
- The half-life of BIVV001 (approximately 27 hrs) was significantly longer than rFVIIIFc or rFVIII for all animal models evaluated. The half-life of BIVV001 was independent of endogenous VWF levels compared to rFVIIIFc or rFVIII.
- rFVIIIFc or rFVIII showed decrease in half-life proportional to VWF status of the animals. Similar trends were observed for other PK parameters (Table 6).

***Reviewer's Note*:**

- *Although FVIII activity was measured in this study, the FVIII activity recovery rate (not the FVIII activity) were compared across the models because the dose levels were different for each molecule administered, therefore it was not possible to make a direct comparison of FVIII activity between animal models. The FVIII recovery rate was normalized to the measured dose value.*

Table 6: PK parameters

Test Article	**Mouse Strain**	**$T_{1/2}$ (hr)**	**C_{max}/ Dose (kg/mL)**	**AUC/ Dose (mL/kg)**	**MRT (hr)**	**Cl (mL/hr/kg)**	**V_{ss} (mL/kg)**
BIVV001	DKO	26.86	0.0220	0.5888	34.32	1.70	58.29
	VWF Heterozygous	29.85	0.0179	0.5730	39.19	1.75	68.40
	HemA	31.77	0.0195	0.6618	41.45	1.51	62.64
	Fold improvement DKO to HemA	1.18	0.89	1.12	1.21	1.12	0.93
rFVIIIFc	DKO	1.85	0.0089	0.0161	2.133 1	62.17	132.62

	VWF Heterozygous	13.21	0.0173	1986	16.42	5.04	82.68
	HemA	16.32	0.0198	0.3511	20.26	2.85	57.71
	Fold improvement DKO to HemA	8.82	2.22	21.81	9.50	21.83	2.30
rFVIII	DKO	0.23	0.0057	0.0025	0.24	407.77	97.32
	VWF Heterozygous	5.43	0.0203	0.1525	7.51	6.56	49.21
	HemA	7.63	0.0217	0.2242	11.04	4.46	49.22
	Fold improvement DKO to HemA	33.17	3.81	89.68	46.24	91.44	1.98

$T_{1/2}$: terminal half-life ;Cmax/Dose: dose normalized maximum activity in plasma; AUC/Dose: dose normalized area under the plasma activity versus time curve; MRT: mean residence time; CL: clearance; ; V_{ss}: volume of distribution at steady state; n = 3-4 animals per group
Source: Report No. R-BV001-11; Module 4.2.2.7 in the BLA

Overall conclusions from the study report:
Per the study report, these results confirmed that the PK of BIVV001 is independent of circulating VWF levels. These results also support the proposed mechanism of action of BIVV001, specifically, the structural design features (i.e., the introduction of D'D3 domain) decouple FVIII from VWF-mediated clearance, thereby removing the half-life limitation imposed by circulating endogenous VWF in BIVV001 compared to first generation long acting rFVIII and rFVIIIFc.

Study #11

Report Number		R-BV001-14
Date Report Signed		04/27/2018
Title		Comparability Pharmacokinetics Study of Three Batches of BIVV001 in Hemophilia A Mice: (b) (4)
GLP Status		No
Testing Facility		Bioverativ, Waltham, MA
Objective(s)		To compare the PK profiles of the toxicology and clinical lots to the final clinical lot of BIVV001.
Study Animals	**Strain/Breed**	Factor VIII KO (HemA) mice
	Species	Mouse
	Age	7-10 weeks
	Body Weight	20-30 gm
	# mice/group	12/group; 4/group/timepoint
	Total #	36
Test Article		BIVV001 • Lot# (b) (4) ((b) (4) scale DS, Lot used in toxicology studies) • Lot# (b) (4) ((b) (4) DS; Manufactured for the Phase 1/2a trial) • Lot# (b) (4) ((b) (4) DS; Manufactured for the Phase 3 trial and intended for commercialization)
Route of Administration		IV injection; tail vein
Description of the Disease Model		HemA mice

Study Groups and Dose Levels	**BIVV001 Dosing Group**	**Target Dose Level (IU/kg)**	**# of Mice**	**Collection Time Points (4 mice/group/timepoint)**
	(b) (4) DS	(b) (4)	12	(b) (4)
	(b) (4) DS		12	
	(b) (4) DS		12	
	***Reviewer's Note*:** ➢ *The target dose was 50 IU/kg based on each lot's aPTT assay activity.* ➢ *The study report does not provide information on how the 4/mice/group/timepoint were selected for blood collection.*			
Dosing Regimen	Single			
Randomization	Yes; based on body weight and age			
Description of Masking	Not provided			
Scheduled Sacrifice Time Points	Not provided in the report. ***Reviewer's Note**:* ➢ *This reviewer assumes that the animals were euthanized following the last blood collection timepoint.*			

***Key Evaluations and Assessments**:*

- FVIII activity was determined by chromogenic assay
- PK profile
    - Blood samples were collected via retro-orbital collection

Key Results:

- FVIII activity was comparable between the three lots of BIVV001at the timepoints evaluated (Table 7).

Table 7: Mean plasma FVIII activity data post IV administration of 50 IU/kg BIVV001(toxicology and clinical lots) in HemA mice

	Time (hrs) Post-dose	**0.083**	**3**	**6**	**24**	**48**	**72**	**96**	**120**	**FVIII dose (IU/kg)**
Mean FVIII Plasma Activity	(b) (4) **(mIU/ml)**	1035.0	882.1	788.9	371.1	106.3	106.6	45.2	32.1	44.4
	(b) (4) **(mIU/ml)**	964.0	723.0	707.5	338.0	144.7	102.1	44.9	19.0	44.7
	(b) (4) **(mIU/ml)**	905.1	754.2	696.0	364.9	155.4	88.8	38.8	27.4	44.6

Source: Report No. R-BV001-14; Module 4.2.2.7 in the BLA

- PK profiles were comparable between the three lots of BIVV001 (Table 8).

Table 8: PK parameters of intravenously dosed BIVV001 (based on product-specific standard) in Hem A mice

BIVV001	Dose	$T_{1/2}$ (hr)	C_{max} (IU/dL)	C_{max}/ Dose (kg/dL)	AUC/ Dose (hr*kg/mL)	Cl (mL/hr/kg)	MRT (hr)	Vss (mL/kg)
(b) (4)	50	26.8	103.5	2.33	0.67	1.5	34.2	50.8
(b) (4)	50	24.9	96.4	2.15	0.59	1.7	33.6	56.5
(b) (4)	50	25.3	90.5	2.02	0.60	1.7	32.9	54.5
Ratios of PK Parameters								
(b) (4)		**1.09**	**1.07**	**1.08**	**1.12**	**0.88**	**1.02**	**0.90**
(b) (4)		**1.02**	**0.94**	**0.94**	**1.01**	**1.00**	**0.98**	**0.96**
(b) (4)		**0.94**	**0.87**	**0.87**	**0.89**	**1.13**	**0.96**	**1.07**

Source: Report No. R-BV001-14; Module 4.2.2.7 in the BLA

Overall Conclusions from the Study Report:
The PK profiles of IV administered BIVV001 in HemA mice were consistent between different lots of BIVV001.

Study #12

Report Number		PD15-118
Date Report Signed		12/30/2016
Title		BIIB073: An Acute Intravenous Injection Pharmacokinetic Study in Male (b) (4) Rats
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To determine the PK profile BIVV001 following a single dose by IV injection in (b) (4) rats
Study Animals	**Strain/Breed**	(b) (4)
	Species	Rat
	Age	8 weeks
	Body Weight	195-219 gm
	# males/group	Groups 1-3: 9/group Group 4: 10/group
	Total #	37
Test Articles		BIVV001 (BIIB073 (b) (4)); Lot# (b) (4) BIVV001 (BIIB073 (b) (4)); Lot# (b) (4) ***Reviewer's Notes*:** ➢ *BIVV001 (BIIB073 (b) (4)) was generated from research cell line (b) (4) and used in Study #6 and Study #10 reviewed in this memo.* ➢ *BIVV001 (BIIB073 (b) (4)) was produced from research grade material, which contained (b) (4) XTEN polypeptide attached to D'D3 compared to the final BIVV001 DP. Per the applicant, these (b) (4) do not impact the PK or PD of the molecule.*
Control Article		Advate®; Lot# (b) (4)
Route of Administration		IV injection; tail vein

Study Groups and Dose Levels	<table><tr><th>Group</th><th>Test Article</th><th>Dose Level (IU/kg/dose)</th></tr><tr><td>1</td><td>Advate®</td><td>150</td></tr><tr><td>2</td><td>BIVV001 (BIIB073 (b) (4))</td><td>150</td></tr><tr><td>3</td><td>BIVV001 (b) (4)</td><td>150</td></tr><tr><td>4</td><td>Naïve (not dosed)</td><td>N/A</td></tr></table> **Note:** Dose level was determined by chromogenic assay.
Dosing Regimen	Single
Randomization	Yes; based on body weight
Description of Masking	Not provided
Scheduled Sacrifice Time Points	Day 6 for Groups 1-3; Day 1 for Group 4

Key Assessments:

- Mortality/Moribundity (twice daily); Clinical observations (daily), body weights (once pre-dose [at randomization], one day before dosing, and at Day 6)
- Blood was collected via jugular venipuncture (n=3/timepoint)
    - Group 1: 0, 0.25, 1, 2, 4, 8, 24, 48, 32, 48 hrs post-dose
    - Groups 2 and 3: 0, 0.25, 4, 8, 24, 48, 32, 48 72, 96, 120 hrs post-dose
- Plasma BIVV001 concentration and FVIII activity were determined by capture chromogenic assay and (b) (4)
- PK profile

***Reviewer's Note*:**

- *Due to circulating endogenous FVIII in the rats, FVIII activity levels were measured by a* (b) (4) *chromogenic assay. In this assay, the dosed FVIII molecule was captured using a* (b) (4) *before conducting the FVIII chromogenic activity assay. However, the* (b) (4) *chromogenic assay used a formulation buffer that did not use* (b) (4) *which resulted in instability of the product and variability in the results using this assay. Therefore, the reported results are from the* (b) (4)

Key Results:

- There were no adverse events reported for any in-life parameters in this study.
- FVIII activity was similar between both lots of BIVV001 and Advate®.
- PK Profile
    - BIVV001 displayed a half-life that was 2-3-fold longer than Advate®.
        - $T_{1/2}$
            - Group 1: 8.4 hours
            - Group 2: 23.6 hours
            - Group 3: 17.2 hours

Study #13

Report Number	P073-16-03
Date Report Signed	12/22/2016
Title	BIIB073: An *In Vivo* Assessment of Pharmacokinetics Following Intravenous Administration in Male (b) (4) Monkeys
GLP Status	No
Testing Facility	(b) (4)

<table>
<tr><td colspan="2">Objective(s)</td><td>To determine the PK profile of BIVV001 following a single IV injection to monkeys.</td></tr>
<tr><td rowspan="6">Study Animals</td><td>Strain/Breed</td><td>(b) (4)</td></tr>
<tr><td>Species</td><td>Monkey</td></tr>
<tr><td>Age</td><td>2-4 years</td></tr>
<tr><td>Body Weight</td><td>1.5-2.6 kg</td></tr>
<tr><td># male/group</td><td>4/group</td></tr>
<tr><td>Total #</td><td>8</td></tr>
<tr><td colspan="2">Test Article</td><td>BIVV001; Lot# (b) (4)</td></tr>
<tr><td colspan="2">Route of Administration</td><td>IV injection</td></tr>
<tr><td colspan="2">Study Groups and Dose Levels</td><td>
<table>
<tr><th>Group</th><th>Test Article</th><th>Dose Level (IU/kg)</th><th>Dose Volume (mL/kg)</th><th>Dose Concentration (IU/mL)</th><th>No. of animals</th></tr>
<tr><td>1</td><td>BIVV001</td><td>100[a]</td><td>2</td><td>50</td><td>4</td></tr>
<tr><td>2</td><td>BIVV001</td><td>300[b]</td><td>2</td><td>150</td><td>4</td></tr>
</table>
[a] Refers to a dose level of 0.0138 mg/kg calculated based on a solution of BIVV001 at a concentration of 0.5 mg/mL and 3615 IU/mL.
[b] Refers to a dose level of 0.0415 mg/kg calculated based on a solution of BIVV001 at a concentration of 0.5 mg/mL and 3615 IU/mL.
</td></tr>
<tr><td colspan="2">Dosing Regimen</td><td>Single</td></tr>
<tr><td colspan="2">Randomization</td><td>Yes; based on body weight</td></tr>
<tr><td colspan="2">Description of Masking</td><td>Not provided</td></tr>
<tr><td colspan="2">Scheduled Sacrifice Time Points</td><td>None</td></tr>
</table>

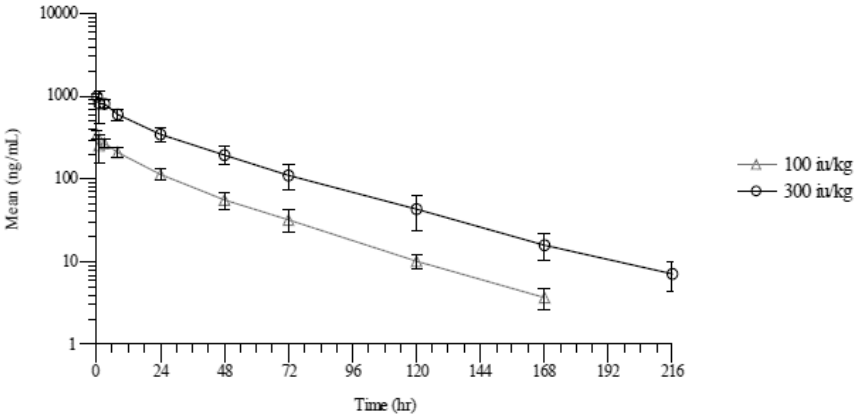
Key Assessments:

- Mortality/Moribundity (twice daily); Cage-side observations (once during pretreatment and daily), clinical observations (weekly during pretreatment), physical examination (once pretreatment), body weights (at least every 2 weeks during pretreatment and at the end of the study)
- Blood was collected via peripheral vein (0, 0.25, 1, 3, 8, 24, 48, 72, 120, 168 and 216 hrs post-dose)
- Plasma BIVV001 concentration was determined by (b) (4)
- FVIII activity was determined by chromogenic assay
- PK profile

Key Results:

- There were no test article-related observations for any study parameters.
- BIVV001 was detected in all dosed monkeys following an IV administration on Day 1.
- BIVV001 was quantifiable up to 168 hrs post-dose in Group 1 and throughout the 216 hour sampling period in Group 2.
- BIVV001 plasma concentrations decreased in dose- and time-dependent manners (Figure 2).

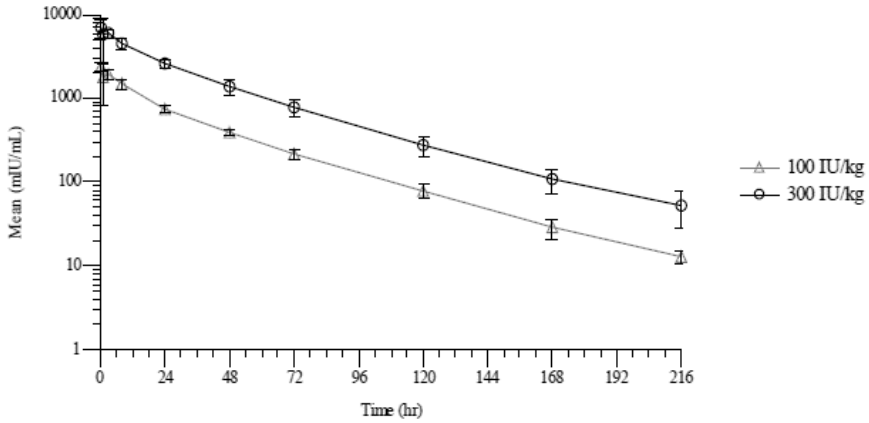
Figure 2: Mean Plasma BIVV001 Concentrations Following Single IV administration of 100 or 300 IU/kg BIVV001



Open triangles indicate the mean BIVV001 concentrations (±SD) for animals receiving a single IV dose of100 IU/kg BIVV001. Open circles indicate the mean BIVV001 concentration (±SD) for animals receiving a single IV dose of 300 IU/kg BIVV001.
Source: Report No. P073-16-03; Module 4.2.2.7 in the BLA

- BIIV001 activity was dose-proportional (Figure 3).

Figure 3: Mean Plasma BIVV001 Activity Following Single IV Administration 100 or 300 IU/kg BIVV001



Open triangles indicate the mean BIVV001 activity (±SD) for animals receiving a single IV dose of100 IU/kg BIVV001. Open circles indicate the mean BIVV001 activity (±SD) for animals receiving a single IV dose of 300 IU/kg BIVV001.
Source: Report No. P073-16-03; Module 4.2.2.7 in the BLA

- PK analysis:
  - $T_{1/2}$:
    - 100 IU/kg BIVV001: 29.3 hrs
    - 300 IU/kg BIVV001: 34.0 hrs

Table 9: Mean PK Parameters in Following a Single 100 IU/kg or 300 IU/kg IV Administration of BIVV001

BIVV001 Dose Level (IU/kg)	**T_{max}** hr	**C_{max}** ng/mL	**AUC** Hr*ng/mL	**AUC/Dose** Hr*ng/mL(IU/kg)	**$T_{1/2}$** hr	**MRT** hr	**CL** mL/hr/kg	**V_d** mL/kg
100	0.25	345	9070	90.7	29.3	32.5	1.52	63.9
SD	-	*42.2*	*1130*	*11.3*	*1.26*	*3.30*	*0.205*	*7.66*
300	0.25	1000	29500	98.4	34.0	38.5	1.45	70.5
	-	*93.9*	*6950*	*23.2*	*1.91*	*3.04*	*0.332*	*13.4*

Source: Report No. P073-16-03; Module 4.2.2.7 in the BLA

***Reviewer's Note*:**

- *Per the applicant, the estimated volume of distribution during terminal phase (V_d) values suggested that BIVV001 was not extensively distributed beyond the vasculature.*

TOXICOLOGY STUDIES

Summary List of Toxicology Studies

The following toxicology studies were conducted to evaluate the safety of ALTUVIIIO™ following administration in various animal species.

Toxicology Studies:

Study Number	**Study Title / Publication Citation**	**Report Number**
14	BIIB073: A 4-Week Repeat Dose Toxicity Study of BIIB073 by Intravenous Injection in the (b) (4) Rat with a 14-Day Recovery Period	P073-16-02
15	BIIB073: A 4-Week Repeat Dose Toxicity Study of BIIB073 by Intravenous Injection in the (b) (4) Monkey with a 21-Day Recovery Period	P073-16-01

Developmental and Reproductive Toxicology Studies:

Per the applicant, developmental and reproductive toxicology studies were not conducted because there were no BIVV001-related effects in the male and female reproductive tissues of rats or monkeys given repeat IV administrations of BIVV001, based on the results in Study #14 (P073-16-02) and Study #15 (P073-16-01).

Genotoxicity Studies:

Per the applicant, genotoxicity studies were not conducted because given the molecular weight (>100 kD), structure, and mechanism of action of BIVV001, it is not likely to cross cellular and nuclear membranes as an intact molecule to directly interact with and damage DNA.

Carcinogenicity/Tumorigenicity Studies:

Per the applicant, studies were not conducted to evaluate this safety endpoint because BIVV001 is a replacement therapy for a human endogenous protein and existing experience from other recombinant FVIII replacement products have not raised concerns regarding carcinogenic or mutagenic effects.

Other Safety/Toxicology Studies

Study Number	Study Title / Publication Citation	Report Number
16	*In Vitro* Evaluation of the Influence of BIIB073 on Human Whole Blood Hemolysis and Plasma Flocculation	P073-16-04

Overview of Toxicology Studies

Study #14

Report Number		P073-16-02
Date Report Signed		04/13/2017
Title		BIIB073: A 4-Week Repeat Dose Toxicity Study of BIIB073 by Intravenous Injection in the (b) (4) Rat with a 14-Day Recovery Period
GLP Status		Yes; per OECD ***Reviewer's Note*:** • *Per the study report, characterization of the test and reference articles were not conducted per GLP.*
Testing Facility		(b) (4)
Objective(s)		To evaluate the toxicity of BIVV001 after repeat IV administration every 3 days for 4 weeks, to determine the reversibility and/or delayed occurrence of any findings over a 2-week treatment-free period, and to determine the toxicokinetic characteristics of BIVV001.
Study Animals	**Strain/Breed**	(b) (4)
	Species	Rat
	Age	7 weeks old
	Body Weight	Males: 203-291 gr Females: 156-218 gr
	#/sex/group	Please refer to 'Study Groups and Dose Levels.'
	Total #	180
Test Article(s)		BIVV001; Lot# (b) (4)
Control Article(s)		Vehicle: 10 mM histidine, 250 mM arginine HCl, 5% sucrose, 5 mM CaCl2, 0.05% PS80; Lot# (b) (4)
Route of Administration		IV injection; tail vein
Study Groups and Dose Levels		See table below
Dosing Regimen		Repeat IV administration; every 3 days from days 1-28 for a total of 10 doses

Group	Test Article	Dose Level (IU/kg/dose)	Animal Numbers					
			Main		Recovery		Toxicokinetic (TK)	
			M	F	M	F	M	F
1	Vehicle	0	10	10	5	5	3	3
2	BIVV001	75	10	10	0	0	9	9
3	BIVV001	250	10	10	0	0	9	9
4	BIVV001	750	10	10	5	5	9	9

• All animals were dosed at a volume of 2mL/kg of BIVV001.

Randomization	Yes; based on body weight
Description of Masking	Not provided
Scheduled Sacrifice Time Points	Days 29 (Main groups) Day 43 (Recovery groups)

Key Assessments:

- Clinical observations (pre-dose, on dosing days, and 1 and 2 hrs post-dose), mortality (twice daily), food consumption (weekly), body weights (weekly), ophthalmology (before randomization for all groups and on days 23 or 24 [Main and Recovery groups])
- Clinical pathology: Hematology, clinical chemistry, coagulation (at necropsy), urinalysis (days 28 and 42)
- TK profile (3/sex/group; days 1, 13, 28 [all groups] and the following hrs post-dose: 0.25, 2, 8, 24, 48, and 72 hrs [BIIV001-dosed animals] and 0.25 and 24 hrs [vehicle-dosed animals]): Plasma concentration of BIVV001 was determined by a validated (b) (4)
- Anti-drug antibodies ([ADA] 3/sex/group): day 29 [Main group]; day 43 [Recovery group], and days 13 and 28 [TK group]): Plasma anti-BIVV001 antibodies were determined by a validated (b) (4)
- Organ weights, gross pathology, histopathology (day 29 [Main group] and day 43 [Recovery group])

Key Results*:*

- No test article-related mortality or adverse effects on any parameter was observed.
- In one Group 4 female rat (Recovery group), a mass at the urogenital level was observed on Days 29, 36 and 43.
    - The same animal had higher neutrophil and monocyte counts, decreased red blood cell count, and hemoglobin that resulted in higher mean values for these parameters in other Recovery Group 4 female animals.
    - The mass determined by a clinical pathologist to be an ulcerated adenocarcinoma of the mammary gland. Per the pathology report, this finding was considered an uncommon spontaneous finding.

***Reviewer's Note*:**

- *Based on review of the data and the pathology report, this reviewer agrees with the clinical pathologist's conclusion.*

- Plasma concentrations of BIVV001 were dose-proportional.

Table 10: BIVV001 TK Profile

Sex	Group	C_{max} (mIU/mL)	AUC (mIU*hr/mL)	AUC/Dose (mIU*hr/mL)/(IU/kg/dose)	$T_{1/2}$ (hr)
M	2	2170	37500	501	17.0
	3	7780	139000	557	20.0
	4	22100	382000	509	22.6
F	2	1870	32200	429	17.8
	3	5930	95900	384	20.6
	4	16200	365000	487	18.5

Source: Toxicology written summary; Module 2.6.6 in the BLA

- Development of ADAs to human FVIII occurred in Groups 2-4. Anti-FVIII antibody formation was dose-proportional and persisted up to the Day 43 timepoint.
- Per the study report and the independent pathologist, no histological abnormalities were evident in the brain, kidneys, liver, lungs, testes, seminal organs, epididymis, or other tissues and organs evaluated.
- The NOAEL was 750 IU/kg/administration, the highest dose level evaluated in the study.

Study #15

Report Number		P073-16-01
Date Report Signed		04/20/2017
Title		BIIB073: A 4-Week Repeat Dose Toxicity Study of BIIB073 by Intravenous Injection in the (b) (4) Monkey with a 21-Day Recovery Period
GLP Status		Yes; per OCED ***Reviewer's Note*:** • *Per the study report, characterization of the test and reference articles were not conducted per GLP.* • *The bleeding worksheet for females in all groups at the 1-hour post time on Day 29 were not found in the raw data and therefore, the actual collection time for these animals at the 1-hour time point could not be confirmed. Based on the TK sampling processing sheet, the centrifugation for these samples was performed within 16 minutes of the target nominal time point.*
Testing Facility		(b) (4)
Objective(s)		To evaluate the toxicity of repeat IV administration of BIVV001 every 4 days for 4 weeks, the reversibility and/or delayed onset of any findings over a 3-week treatment free period, and to determine the TK characteristics of BIVV001.
Study Animals	**Strain/Breed**	(b) (4)
	Species	(b) (4) Monkey
	Age	2-3 years old
	Body Weight	2.4 to 3.5 kg
	#/sex/group	Main Group: 4/sex/group Recovery Group: 2/sex/group
	Total #	50
Test Article(s)		BIVV001; Lot# (b) (4) ***Reviewer's Note*:** • *This lot number is listed as Lot#* (b) (4) *in the study report.*
Control Article(s)		Vehicle: 10 mM histidine, 250 mM arginine HCl, 5% sucrose, 5 mM CaCl2, 0.05% PS80; Lot# (b) (4)
Route of Administration		IV injection

<table>
<tr><td>Study Groups and Dose Levels</td><td>
<table>
<tr><th rowspan="3">Group</th><th rowspan="3">Test Article</th><th rowspan="3">Dose Level (IU/kg/dose)</th><th colspan="4">Animal Numbers</th></tr>
<tr><th colspan="2">Main</th><th colspan="2">Recovery</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>1</td><td>Vehicle</td><td>0</td><td>4</td><td>4</td><td>0</td><td>0</td></tr>
<tr><td>2</td><td>BIVV001</td><td>25</td><td>4</td><td>4</td><td>0</td><td>0</td></tr>
<tr><td>3</td><td>BIVV001</td><td>75</td><td>4</td><td>4</td><td>2</td><td>2</td></tr>
<tr><td>4</td><td>BIVV001</td><td>250</td><td>4</td><td>4</td><td>0</td><td>0</td></tr>
<tr><td>5</td><td>BIVV001</td><td>750</td><td>4</td><td>4</td><td>2</td><td>2</td></tr>
</table>
• All BIVV001 animals were dosed at a volume of 2mL/kg.
</td></tr>
<tr><td>Dosing Regimen</td><td>Repeat IV administration; once every 4 days for a total of 8 doses</td></tr>
<tr><td>Randomization</td><td>Yes; based on body weight</td></tr>
<tr><td>Description of Masking</td><td>Not provided</td></tr>
<tr><td>Scheduled Sacrifice Time Points</td><td>Days 33 (Main groups) Day 50 (Recovery groups)</td></tr>
</table>

Key Assessments:

- Physical examination (pre-dose, once during last week of dosing and recovery) Clinical observation (twice daily on dosing days), mortality/morbidity (twice daily), food consumption (daily), body weights (weekly), ophthalmology (pre-dose and at week 4), Electrocardiology (twice at baseline, 0.5 hrs after dosing, on days 9 and 25, and local irritation assessment (on days of dosing: pre-dose and 4 hrs post-dose; weekly for Recovery groups)
- Clinical pathology: Hematology, clinical chemistry, coagulation (at necropsy), urinalysis (days 28 and 42)
- TK profile (days 1, 13, 28 [all groups] and the following hrs post-dose: 0.25, 2, 8, 24, 48, and 72 hrs [BIIV001-dosed animals] and 0.25 and 24 hrs [vehicle dosed animals]): Plasma concentration of BIVV001 was determined by a validated (b) (4)
- ADAs (pre-dose day 1, 13, 33, and 50): Plasma anti-BIVV001 antibodies were determined by a validated (b) (4)
- Organ weights, gross pathology, histopathology (day 33 [Main group] and day 50 [Recovery group])

Key Results*:*

- One Group 5 male animal was found dead on Day 30. The death was test article-related and attributed to blood loss secondary to venipuncture and impaired hemostasis caused by ADA-induced acquired hemophilia.
    - Swollen soft right inguinal area was noted on Day 29
    - Gross pathology finding of swelling and dark discoloration were noted in the hind limbs. Some internal organs (lung and small intestine [duodenum, jejunum]) were also described as pale and the spleen appeared enlarged grossly.
    - Blood clot in the skeletal muscle of the left hind limb and scrotum and dark focal in the injection site area that extended into the perivascular tissue. Histological examination of these lesions showed acute, diffuse and severe hemorrhage.
    - Prolonged aPTT on Day 13 (34.7 seconds) and on Day 29 (47.8 seconds) and decreased FVIII activity measured from Day 1 to Day 29 were consistent with the development of neutralizing antibodies.

- No mortality or adverse effects on any other in-life parameter was observed for any other animal throughout the study.
    - Higher values in creatine kinase (CK) activity observed in Groups 2-5 (18% to 622% higher than pre-dose values) after the main phase of the study. Higher CK values persisted only in Group 5 females following the recovery period (434% higher than pre-dose).
    - Higher aspartate aminotransferase (AST) activity (15% to 103%) in males given Groups 2-5 and in Groups 4-5 females following the main phase; elevated AST values did not persist following the recovery period.

***Reviewer's Note*:**

- *Per the study report, the elevated CK and AST values were not associated with any histological correlate or changes in organ weight, and showed individual variability in the values; therefore, these were not considered adverse by the independent pathologist.*

- *aPTT prolongation was observed in Groups 2-5 compared to Group 1 (Table 11).*

Table 11: Mean aPTT values from the 4-week repeat-dose toxicology study in monkeys

		Group Number									
		1		2		3		4		5	
	Day	M	F	M	F	M	F	M	F	M	F
Mean aPTT values	13	22.08	21.55	22.15	23.68	23.9	22.9	23.98	22.1	28.32	22.55
	33	21.03	23.25	22.18	24.5	31.78	26.73	34.57	25.6	35.73	31.6
	50	N/A	N/A	N/A	N/A	24.3	22.75	N/A	N/A	26.5	34.55

N/A: not applicable because there were no recovery animals assigned to dose group
Source: Toxicology written summary; Module 2.6.6 in the BLA

- Development of ADAs occurred in Groups 2-5. Anti-FVIII antibody formation was dose-dependent and persisted up to the Day 50 (Table 12).

Table 12: Summary of ADA development

Group	No. (%) screened + on Day 1 or Day 13*	No. (%) confirmed + on Day 33*	No. (%) confirmed + on Day 50
1	1/8 (12.5)	1/8 (12.5)	N/A
2	6/8 (75)	2/8 (25)	N/A
3	10/12 (83.3)	8/12[a] (66.7)	3/4 (75)
4	8/8 (100)	8/8 (100)	N/A
5	12/12 (100)	11/12[b] (91.7)	2/3[c]

N/A: not applicable because there were no recovery animals assigned to dose group
*Number of males and females confirmed positive for ADA/Number of total males and females evaluated at that time point; [a] Includes 1 animal positive on Day 1; [b] Excludes analysis from Day 29 TK sample for one recovery monkey; [c] One early death occurred in this recovery group
Source: Toxicology written summary; Module 2.6.6 in the BLA

***Reviewer's Comment*:**

- *aPTT prolongation correlated with presence of ADA in BIVV001 dosed-animals, indicating that ADA formation led to acquired hemophilia.*

- BIVV001 TK profile:

Table 13: BIVV001 TK profile

Sex	Group	C_{max} (mIU/mL)	AUC (mIU*hr/mL)	AUC/Dose (mIU*hr/mL)/(IU/kg/dose)	$T_{1/2}$ (hr)
M	2	1050 (±95.2)	29600 (±4280)	1180 (±171)	33.8 (± 6.1)
	3	3210 (±340)	79900 (±10100)	1070 (±134)	31.0 (±4.6)
	4	11100 (±2320)	28300 (±73300)	1130 (±293)	29.2 (±2.9)
	5	31200 (±4820)	767000 (±144000)	1020 (±192)	29.2 (±3.2)
F	2	1160 (±30)	33400 (±1200)	1340 (±48)	27.8 (±0.5)
	3	3000 (±374)	77600 (±16300)	1030 (217)	27.5 (±2.8)
	4	12400 (±2030)	306000 (±62200)	1220 (±249)	27.0 (±2.2)
	5	32400 (±5960)	799000 (±165000)	1070 ±220)	27.1 (±5.2)

Values in parentheses are SD.
Source: Toxicology written summary; Module 2.6.6 in the BLA

- 1/2 Group 3 male animals had a 5 mm diameter mass on the spleen noted during the scheduled necropsy. The finding correlated microscopically with a hematoma. This finding was attributed to be ADA development as a result of BIVV001 administration.
- No other macroscopic BIVV001-related effects were observed.
- The NOAEL was determined by the study director to be 750 IU/kg/dose.

***Reviewer's Comment*:**

- *Per the study report, the single ADA-associated death and dose-dependent aPTT prolongation were attributed to development of ADA against BIVV001, likely cross reacting with endogenous monkey FVIII. This reviewer agrees with the conclusion of the study report regarding the cause of the aPTT prolongation and mortality. However, based on the adverse findings in the group administered 750 IU/kg/dose, this reviewer considers the NOAEL for this study to be 250 IU/kg/dose.*

Study #16
***In Vitro* Evaluation of the Influence of BIIB073 on Human Whole Blood Hemolysis and Plasma Flocculation** (Study Report # P073-16-04; (b) (4) (b) (4) per OECD Principles of GLP; date signed 05/29/2020)

Objective:
To evaluate the effect of BIVV001on hemolysis and plasma flocculation (turbidity) in human whole blood *in vitro*.

Methods:
Whole blood samples were collected from 3 male and 3 female human healthy subjects. Blood samples were divided in aliquots and treated with control reagents (b) (4) (b) (4) or BIVV001 (b) (4) (b) (4) and incubated for (b) (4) at (b) (4)

- Hemolysis was evaluated by determination of whole blood hematocrit, whole blood hemoglobin concentration, plasma hemoglobin concentration, plasma hemolytic index, and visual macroscopic hemolysis assessment.
- Flocculation was evaluated by determination of the plasma turbidity index and visual flocculation assessment.

Results:
No hemolysis and no flocculation were observed following *in vitro* treatment of human whole blood with BIVV001 at the concentrations evaluated.

APPLICANT'S PROPOSED LABEL

Section 8 ('Use in Specific Populations') complies with 21 CFR 201.56(d)(1), 201.57(c)(9). And 201.57(c)(14); minor edits will be recommended.

Section 13.1 ('Carcinogenesis, Mutagenesis, Impairment of Fertility') is generally acceptable, but edits to make the statements more concise will be recommended.

Section 13.2 ('Animal Toxicology and/or Pharmacology') is currently not included in the label.

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data support approval of the license application.

KEY WORDS/TERMS

Hemophilia A, FVIII, ALTUVIIIO™, efanesoctocog alfa, rFVIIIFc-VWF-XTEN, BIIB073, BIVV001, Advate®, Hem A mice, rats, monkeys, aPTT, coagulation, pharmacokinetic, toxicity, intravenous, immunogenicity, pharmacology